

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing:

21 October 1999 (21.10.99)

International application No.:

PCT/IL98/00586

Applicant's or agent's file reference:

114901.2 RS

International filing date:

01 December 1998 (01.12.98)

Priority date:

04 December 1997 (04.12.97)

Applicant:

GABIZON, Alberto, A. et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

06 May 1999 (06.05.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel Aviv
ISRAËL

Date of mailing (day/month/year) 13 June 2000 (13.06.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 114901.2 RS	
International application No. PCT/IL98/00586	International filing date (day/month/year) 01 December 1998 (01.12.98)

1. The following indications appeared on record concerning:

☒ the applicant

 ☐ the inventor

 ☐ the agent

 ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person

 ☐ the name

 ☐ the address

 ☐ the nationality

 ☐ the residence

Name and Address HADASIT MEDICAL RESEARCH SERVICES AND DEVELOPMENT LTD. Kiryat Hadassah P.O. Box 12000 91120 Jerusalem Israel	State of Nationality IL	State of Residence IL
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

Co-applicant for all designated States except US.

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

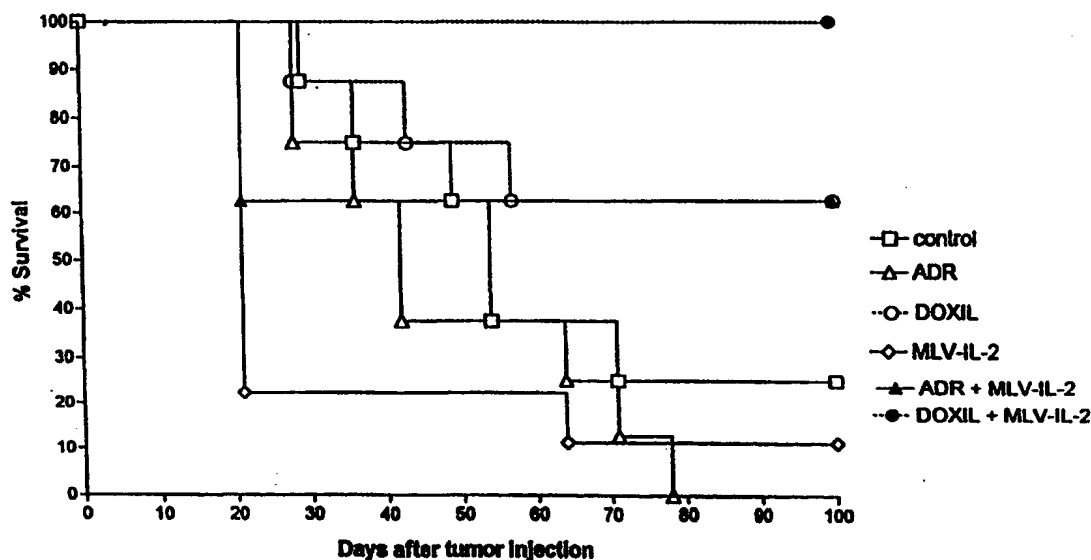
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Marie-José Devillard Telephone No.: (41-22) 338.83.38
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/127, 38/19		A1	(11) International Publication Number: WO 99/27908
			(43) International Publication Date: 10 June 1999 (10.06.99)
(21) International Application Number: PCT/IL98/00586		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 1 December 1998 (01.12.98)			
(30) Priority Data: 60/067,697 4 December 1997 (04.12.97) US			
(71) Applicant (for all designated States except US): YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, 91042 Jerusalem (IL).			
(72) Inventors; and (75) Inventors/Applicants (for US only): GABIZON, Alberto, A. [IL/IL]; Bernstein Street 56/7, 96920 Jerusalem (IL). KEDAR, Eliezer [IL/IL]; Kadish Luz Street 24/7, 96920 Jerusalem (IL). BARENHOLZ, Yechezkel [IL/IL]; Nave Shanan Street 18, 93707 Jerusalem (IL).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(74) Agent: REINHOLD COHN AND PARTNERS; P.O. Box 4060, 61040 Tel Aviv (IL).			

(54) Title: COMBINED CHEMO-IMMUNOTHERAPY WITH LIPOSOMAL DRUGS AND CYTOKINES



(57) Abstract

A method of antitumor therapy is described in which administration of a chemotherapeutic drug, encapsulated in liposomes, is supplemented by administration of an immunostimulating cytokine. The cytokine is preferably also encapsulated in liposomes. In tumor models for lung and colon carcinomas, this method produced a significantly greater therapeutic effect, as evidenced by survival rate and tumor size, than a combination of the effects produced by the free or liposome-encapsulated components administered individually.

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EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

In International Application No

PCT/IL 98/00586

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/127 A61K38/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 546 951 A (THE LIPOSOME COMPANY, INC.) 16 June 1993 see page 3, line 39 - page 4, line 5 see page 7, line 20 - line 28 see claims 1-10 ---	1, 2, 4, 6, 10, 13, 23, 26-29
Y	DE 44 30 593 A (MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN) 22 February 1996 see claim 19 ---	1, 2, 4, 6, 10, 13, 23, 26-29
A	WO 90 13293 A (SYRACUSE UNIVERSITY) 15 November 1990 see page 15, line 6 - page 16, line 9 see page 18, line 15 - line 27 see page 21, line 19 - line 38 --- -/--	1-30



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 May 1999

Date of mailing of the international search report

19/05/1999

Name and mailing address of the ISA

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Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 98/00586

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Week 8814 Derwent Publications Ltd., London, GB; AN 88-096332 XP002102116 & JP 63 048225 A (GREEN CROSS CORP) , 29 February 1988 see abstract</p> <p style="text-align: center;">---</p>	2,15
A	<p>EP 0 433 765 A (CONSIGLIO NAZIONALE DELLE RICERCHE) 26 June 1991 see claims 1,2,4</p> <p style="text-align: center;">---</p>	2,15
A	<p>WO 85 00968 A (HEALTH RESEARCH, INC.) 14 March 1985 see claim 1</p> <p style="text-align: center;">---</p>	1-22
A	<p>WO 91 05545 A (LIPOSOME TECHNOLOGY, INC.) 2 May 1991</p> <p>see claims 1,9 & US 5 013 556 A cited in the application</p> <p style="text-align: center;">---</p>	3-5,10, 11,20, 21,29,30
A	<p>WO 91 05546 A (LIPOSOME TECHNOLOGY, INC.) 2 May 1991</p> <p>see claims 7,8 & US 5 013 556 A cited in the application</p> <p style="text-align: center;">-----</p>	3-7,9, 14, 16-18, 25-28

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 98/00586

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-22
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL 98/00586

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 546951	A	16-06-1993	NONE	
DE 4430593	A	22-02-1996	WO 9605821 A EP 0776202 A	29-02-1996 04-06-1997
WO 9013293	A	15-11-1990	CA 2031520 A EP 0429585 A JP 3505744 T	29-10-1990 05-06-1991 12-12-1991
EP 433765	A	26-06-1991	IT 1238231 B JP 4009338 A	12-07-1993 14-01-1992
WO 8500968	A	14-03-1985	EP 0153955 A US 4873088 A	11-09-1985 10-10-1989
WO 9105545	A	02-05-1991	US 5013556 A AT 115401 T AT 122229 T AU 642679 B AU 6637490 A AU 654120 B AU 6898291 A CA 2067133 A,C CA 2067178 A,C DE 69015207 D DE 69015207 T DE 69019366 D DE 69019366 T DK 496835 T EP 0496813 A EP 0496835 A ES 2071976 T FI 921763 A FI 921764 A GR 3017060 T HK 14097 A IL 96069 A IL 96070 A JP 10001431 A JP 2667051 B JP 5501264 T JP 5505173 T KR 134982 B LU 88854 A US 5527528 A WO 9105546 A US 5620689 A US 5225212 A US 5213804 A US 5843473 A US 5356633 A	07-05-1991 15-12-1994 15-05-1995 28-10-1993 16-05-1991 27-10-1994 16-05-1991 21-04-1991 21-04-1991 26-01-1995 04-05-1995 14-06-1995 05-10-1995 17-07-1995 05-08-1992 05-08-1992 01-07-1995 21-04-1992 21-04-1992 30-11-1995 14-02-1997 08-12-1995 30-03-1995 06-01-1998 22-10-1997 11-03-1993 05-08-1993 22-04-1998 11-03-1997 18-06-1996 02-05-1991 15-04-1997 06-07-1993 25-05-1993 01-12-1998 18-10-1994
WO 9105546	A	02-05-1991	US 5013556 A AT 115401 T AT 122229 T AU 642679 B AU 6637490 A AU 654120 B	07-05-1991 15-12-1994 15-05-1995 28-10-1993 16-05-1991 27-10-1994

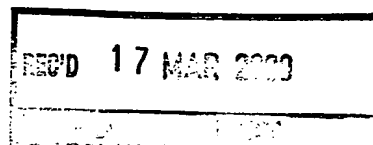
INTERNATIONAL SEARCH REPORT

Information on patent family members

I. International Application No

PCT/IL 98/00586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9105546 A		AU 6898291 A	16-05-1991
		CA 2067133 A,C	21-04-1991
		CA 2067178 A,C	21-04-1991
		DE 69015207 D	26-01-1995
		DE 69015207 T	04-05-1995
		DE 69019366 D	14-06-1995
		DE 69019366 T	05-10-1995
		DK 496835 T	17-07-1995
		EP 0496813 A	05-08-1992
		EP 0496835 A	05-08-1992
		ES 2071976 T	01-07-1995
		FI 921763 A	21-04-1992
		FI 921764 A	21-04-1992
		GR 3017060 T	30-11-1995
		HK 14097 A	14-02-1997
		IL 96069 A	08-12-1995
		IL 96070 A	30-03-1995
		JP 10001431 A	06-01-1998
		JP 2667051 B	22-10-1997
		JP 5501264 T	11-03-1993
		JP 5505173 T	05-08-1993
		KR 134982 B	22-04-1998
		LU 88854 A	11-03-1997
		US 5527528 A	18-06-1996
		WO 9105545 A	02-05-1991
		US 5620689 A	15-04-1997
		US 5225212 A	06-07-1993
		US 5213804 A	25-05-1993
		US 5843473 A	01-12-1998
		US 5356633 A	18-10-1994



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 114901.2 RS	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IL98/00586	International filing date (day/month/year) 01/12/1998	Priority date (day/month/year) 04/12/1997
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF ... et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 06/05/1999	Date of completion of this report 15.03.00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lindner, A Telephone No. +49 89 2399 8640 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IL98/00586

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-30 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IL98/00586

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	14-22
	No:	Claims	1-13, 23-30
Inventive step (IS)	Yes:	Claims	
	No:	Claims	14-22
Industrial applicability (IA)	Yes:	Claims	23-30
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IL98/00586

V:

1. Reference is made to the following documents:

D1 = WO 90/13293
D2 = EP-A-0 546 951
D3 = WO 91/05546
2. D1 discloses liposomes comprising a cytochalasin (antineoplastic agent), optionally in combination with other antineoplastic agents such as doxorubicin, and IL-2 for antitumor therapy (D1: p. 1, l. 22-35; p. 21, l. 19-38). As a consequence, D1 destroys the novelty of independent claims 1 and 23 (article 33(2) PCT).
3. As for present claim 14, it is noted that according to D1, IL-2 administration may be separate from cytochalasin administration (D1: p. 21, l. 1-9). As a consequence, the subject-matter of independent claim 14 does not involve an inventive step over D1 (article 33(3) PCT). In this context, it is noted that the derivation of the liposomal lipids with PEG chains does not appear to cause any non-obvious technical effects. It is further noted that PEG derivatized liposomes comprising antineoplastic agents such as doxorubicin are well known in the prior art (D3: claim 1-6).
4. Reference is also made to D2 which discloses a method for treating tumors by administering conventional liposomes comprising an antineoplastic agent and a non encapsulated hematopoietic cell stimulating agent which is preferably GM-CSF or G-CSF (D2: claims; p. 3, l. 47). As a consequence, the only difference between D2 and the subject-matter as claimed in claim 14 consists in the fact that the liposomes according to the present application contain PEG chains. For the reasons as outlined in paragraph 3 above, no inventive activity can be acknowledged for exchanging the lipids of D2 by the PEG derivatized lipids of the present application. The requirements of article 33(3) PCT are therefore not met.
5. The dependent claims do not contain additional technical features which might establish novelty and an inventive step over D1 (articles 33(2) and 33(3) PCT).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IL98/00586

These claims are only allowable in combination with patentable independent claims.

6. Claims 1-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion is formulated with respect to the industrial applicability of the subject-matter of these claims (article 34(4)(a)(i) PCT).

VIII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.
2. Registered trade marks (cf. claims 9, 18 and 28) should not show in the claims (article 6 PCT).